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**WO 01/15673 A2**

(54) Title: **PHARMACEUTICAL FORMULATIONS AND USE THEREOF IN THE PREVENTION OF STROKE, DIABETES AND/OR CONGESTIVE HEART FAILURE**

(57) Abstract: The present invention relates to use of an inhibitor of the renin-angiotensin system (RAS) or a pharmaceutically acceptable derivative thereof, particularly ramipril or ramiprilat, in the manufacture of a medicament for the prevention of stroke, diabetes and/or congestive heart failure (CHF). The present invention further relates to a method of prevention and/or treatment of stroke, diabetes and/or CHF, comprising administering a therapeutically effective amount of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof, particularly ramipril or ramiprilat, to a patient in need of such prevention and/or treatment.

Pharmaceutical Formulations And Use Thereof In The Prevention Of Stroke,  
Diabetes And/Or Congestive Heart Failure

FIELD OF INVENTION

5       The present invention relates to use of an inhibitor of the renin-angiotensin system (RAS) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the prevention of stroke, diabetes and /or congestive heart failure (CHF). The present invention further relates to a method of prevention and/or  
10      treatment of stroke, diabetes and/or CHF, comprising administering a therapeutically effective amount of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof to a patient in need of such prevention and/or treatment.

BACKGROUND OF THE INVENTION

15       Compounds that interfere with the RAS are well known in the art and are used to treat cardiovascular diseases, particularly arterial hypertension and heart failure. Principally, the RAS can be interferred with by inhibition of the enzymes synthesizing angiotensins or by blocking the corresponding receptors at the effector sites.  
20      Available today are inhibitors of the angiotensin converting enzyme (ACE) and angiotensin II type 1 receptor (AT II) antagonists.

ACE inhibitors are compounds which inhibit the conversion of angiotensin I into the active angiotensin II as well as the breakdown of the active vasodilator bradykinin.  
25      Both of these mechanisms lead to vasodilation. Such compounds have been described in, for example, EP 158927, EP 317878, US 4,743,450, and US 4,857,520.

Ramipril (disclosed in EP-A-079022) is a long-acting ACE inhibitor. Its active  
30      metabolite is the free diacid ramiprilat, which is obtained in vivo upon administration of ramipril. In hypertensive patients administration of ramipril is known to cause a reduction in peripheral arterial resistance and thus a reduction of the blood pressure without a compensatory rise in heart rate. It is currently being used in the treatment of hypertension and CHF. Furthermore, ramipril has been shown to reduce mortality

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in patients with clinical signs of congestive heart failure after surviving an acute myocardial infarction. Ramipril has been suggested to have an added advantage over many other ACE inhibitors due to its pronounced inhibition of ACE in tissues resulting in organ protective effects in e.g. the heart, kidney, and blood vessels.

5

Compounds that interfere with the RAS including ACE inhibitors and AT II antagonists are currently used in the treatment of various cardiovascular disorders, especially in patients exhibiting a high blood pressure. Use of said compounds in prevention of cardiovascular disorders is much less common and the use of said compounds in the prevention of stroke, diabetes and /or CHF is hitherto unknown.

10

#### SUMMARY OF THE INVENTION

The present invention relates to use of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the prevention of stroke, especially in patients exhibiting normal or low blood pressure.

15

The present invention further relates to use of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the prevention of diabetes.

20

The present invention also relates to use of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the prevention of development of CHF in patients with no preexisting CHF, i.e. no signs or symptoms of CHF.

25

Another aspect of the invention is a method of prevention of stroke, diabetes and/or CHF, comprising administering a therapeutically effective amount of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof, to a patient in need of such prevention.

Yet another aspect of the invention is a pharmaceutical formulation for use in the prevention of stroke, diabetes and/or CHF, comprising a therapeutically effective amount of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof.

5

A further aspect of the invention is the use of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof, in the prevention of stroke, diabetes and/or CHF, by administering the inhibitor of the RAS or a pharmaceutically acceptable derivative thereof, to a patient in need of such prevention.

10

#### DETAILED DESCRIPTION OF THE INVENTION

It has surprisingly been found that cardiovascular and metabolic disorders such as stroke, diabetes and CHF can be prevented by use of an inhibitor of RAS, particularly an ACE inhibitor that interferes with the synthesis of angiotensin II. The present invention is especially surprising in that especially patients with an essentially maintained heart function and/or exhibiting a normal or low blood pressure benefit markedly from the preventive action of the inhibitors of RAS. The invention describes a new method to prevent disorders such as stroke, diabetes and/or CHF by administration of an inhibitor of the RAS.

Patients exhibiting a normal or low blood pressure are known as normotensive patients. Examples of guidelines defining blood pressure values for different patient groups including different ages, include guidelines issued by the WHO and JNC (USA). In the present invention, a suitable definition of a normal or low blood pressure can be found in JNC VI, which is hereby incorporated by reference.

In the present invention, "stroke" includes both fatal and non-fatal.

30 In the present invention, "diabetes" include both type I diabetes, also known as insulin-dependent, diabetes mellitus (IDMM), and type II diabetes, also known as non-insulin-dependent diabetes mellitus (NIDDM).

In the present invention, "inhibitor of the renin-angiotensin system (RAS) or a pharmaceutically acceptable derivative thereof" includes any compound which in itself or upon administration blocks the negative effects of angiotensin II on the 5 vasculature either by reducing the synthesis of angiotensin II or blocking its effect at the receptor.

In the present invention, "angiotensin converting enzyme (ACE) inhibitor or a pharmaceutically acceptable derivative thereof" includes any compound which in 10 itself or upon administration interferes with the synthesis of angiotensin II.

When the inhibitor of the RAS used in the present invention have several asymmetric carbon atoms, they can consequently exist in several stereochemical forms. The present invention includes the mixture of isomers as well as the individual 15 stereoisomers. The present invention further includes geometrical isomers, rotational isomers, enantiomers, racemates and diastereomers.

Where applicable, the inhibitors of RAS may be used in neutral form, e.g. as a carboxylic acid, or in the form of a salt, preferably a pharmaceutically acceptable salt 20 such as the sodium, potassium, ammonium, calcium or magnesium salt of the compound at issue. Where applicable the compounds listed above can be used in hydrolyzable ester form.

In the present invention, the inhibitors of the RAS include all prodrugs thereof, 25 whether active or inactive *in vitro*. Thus, although such protected derivatives may not possess pharmacological activity *per se*, they may be administered e.g. parenterally or orally, and thereafter metabolized *in vivo* to form pharmacologically active inhibitors of RAS. Preferred examples are ramipril, which is metabolized into ramiprilat, and candesartan cilexetil, which is metabolized into candesartan.

Inhibitors of the RAS include ACE inhibitors, AT II antagonists, also known as angiotensin receptor blockers (ARBs), renin antagonists, and vasopeptidase inhibitors (VPIs).

- 5 The phrase "vasopeptidase inhibitors" embraces so-called NEP/ACE inhibitors (also referred to as selective or dual acting neutral endopeptidase inhibitors) which possess neutral endopeptidase (NEP) inhibitory activity and angiotensin converting enzyme (ACE) inhibitory activity.
- 10 The phrase "renin antagonists" embraces renin inhibitors.

In the present invention, the RAS inhibitors may exhibit a long term duration, medium term duration or short term duration.

- 15 ACE inhibitors or pharmaceutically acceptable derivatives thereof, including active metabolites, which can be used for the prevention of stroke, diabetes and/or CHF include, but is not limited to, the following compounds:  
alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-20 glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril,
- 25 muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat.

30 Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for uses in the

present invention are ramipril and ramiprilat. Information about ramipril and ramiprilat can be obtained e.g. from the Merck Index., 12<sup>th</sup> ed., 1996, pp. 1394-1395.

AT II antagonists or pharmaceutically acceptable derivatives thereof, including active  
5 metabolites, which can be used for the prevention of stroke, diabetes and/or CHF include, but is not limited to, those described in European Patent Applications, Publication Nos. 253310, 323841, 324377, 399731, 400974, 401030, 403158, 403159, 407102, 407342, 409332, 411507, 411766, 412594, 412848, 415886, 419048, 420237, 424317, 425211, 425921, 426021, 427463, 429257, 430300,  
10 430709, 432737, 434038, 434249, 435827, 437103, 438869, 442473, 443568, 443983, 445811, 446062, 449699, 450566, 453210, 454511, 454831, 456442, 456442, 456510, 459136, 461039, 461040, 465323, 465368, 467207, 467715, 468372, 468470, 470543, 475206, 475898, 479479, 480204, 480659, 481448, 481614, 483683, 485929, 487252, 487745, 488532, 490587, 490820, 492105,  
15 497121, 497150, 497516, 498721, 498722, 498723, 499414, 499415, 499416, 500297, 500409, 501269, 501892, 502314, 502575, 502725, 503162, 503785, 503838, 504888, 505098, 505111, 505893, 505954, 507594, 508393, 508445, 508723, 510812, 510813, 511767, 511791, 512675, 512676, 512870, 513533, 513979, 514192, 514193, 514197, 514198, 514216, 514217, 515265, 515357,  
20 515535, 515546, 515548, 516392, 517357, 517812, 518033, 518931, 520423, 520723, 520724, 521768, 522038, 523141, 526001, 527534, and 528762. Other All antagonists include those disclosed in International Patent Application, Publication Nos. WO 91/00277, WO 91/00281, WO 91/11909, WO 91/11999, WO 91/12001, WO 91/12002, WO 91/13063, 91/15209, WO 91/15479, WO 91/16313, WO  
25 91/17148, WO 91/18888, WO 91/19697, WO 91/19715, WO 92/00067, WO 92/00068, WO 92/00977, WO 92/02510, WO 92/04335, WO 92/04343, WO 92/05161, WO 92/06081, WO 92/07834, WO 92/07852, WO 92/09278, WO 92/09600, WO 92/10189, WO 92/11255, WO 92/14714, WO 92/16523, WO 92/16552, WO 92/17469, WO 92/18092, WO 92/19211, WO 92/20651, WO  
30 92/20660, WO 92/20687, WO 92/21666, WO 92/22533, WO 93/00341, WO 93/01177, WO 93/03018, WO 93/03033 and WO 93/03040. The contents of the

aforesaid European and International Patent Applications are hereby incorporated by reference thereto.

Preferred AT II antagonists or pharmaceutically acceptable derivatives thereof for  
5 use in the present invention include, but is not limited to, compounds with the  
following generic names: candesartan, candesartan cilexetil, losartan, valsartan,  
irbesartan, tasosartan, telmisartan and eprosartan.

Particularly preferred AT II antagonists or pharmaceutically acceptable derivatives  
10 thereof for use in the present invention are candesartan and candesartan cilexetil.  
Candesartan and candesartan cilexetil are known from European Patent No. 459  
136 B1, US 5,196,444 and US 5,703,110 to Takeda Chemical Industries.  
Candesartan cilexetil is currently manufactured and sold world-wide by AstraZeneca  
and Takeda.e.g. under the trade names Atacand®, Amias® and Biopress®.

15 NEP/ACE-inhibitors or pharmaceutically acceptable derivatives thereof, including  
active metabolites, which can be used for the prevention of stroke, diabetes and/or  
CHF include, but is not limited to, those compounds disclosed in U.S. Patents Nos.  
5,508,272, 5,362,727, 5,366,973, 5,225,401, 4,722,810, 5,223,516, 5,552,397,  
20 4,749,688; 5,504,080, 5,612,359, 5,525,723, 5,430,145, and 5,679,671, and  
European Patent Applications 0481522, 0534263, 0534396, 0534492 and 0671172.

Preferred NEP/ACE inhibitors for use in the present invention are those which are  
designated as preferred in the above U.S. patents and European Patent Applications  
25 and are incorporate herein by reference. Especially preferred is the NEP/ACE  
inhibitor omapatrilat (disclosed in U.S. Patent No. 5,508,272), or MDL100240  
(disclosed in U.S. Patent No. 5,430,145).

30 Renin-inhibitors or pharmaceutically acceptable derivatives thereof, including active  
metabolites, which can be used for the prevention of stroke, diabetes and/or CHF  
include, but is not limited to, the following compounds:

enalkrein; RO 42-5892; A 65317; CP 80794; ES 1005; ES 8891; SQ 34017; CGP 29287; CGP 38560; SR 43845; U-71038; A 62198; and A 64662.

### Pharmaceutical formulations

5

In one aspect, the present invention relates to pharmaceutical formulations comprising as active ingredient an RAS inhibitor or a pharmaceutically acceptable derivative or prodrug thereof, including metabolites, for use in the prevention of stroke, diabetes and/or congestive heart failure (CHF).

10

For clinical use, the RAS inhibitor is formulated into a pharmaceutical formulation for oral, intravenous, subcutaneous, tracheal, bronchial, intranasal, pulmonary, transdermal, buccal, rectal, parenteral or some other mode of administration. The pharmaceutical formulation may contain the inhibitor in admixture with a 15 pharmaceutically acceptable adjuvant, diluent and/or carrier.

20

In the preparation of the pharmaceutical formulations of the present invention the active ingredient may be mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating 20 agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture may then be processed into granules or pressed into tablets.

25

The active ingredient may be separately premixed with the other, non-active ingredients, before being mixed to form a formulation.

30

Soft gelatine capsules may be prepared with capsules containing a mixture of the active ingredient of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Hard gelatine capsules may contain granules of the active ingredients. Hard gelatine capsules may also contain the active ingredients in

combination with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine.

Dosage units for rectal administration may be prepared (i) in the form of  
5 suppositories which contain the active substance mixed with a neutral fat base; (ii) in  
the form of a gelatine rectal capsule which contains the active substance in a mixture  
with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules;  
(iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro  
enema formulation to be reconstituted in a suitable solvent just prior to  
10 administration.

Liquid preparations may be prepared in the form of syrups or suspensions, e.g.  
solutions or suspensions containing the active ingredients and the remainder  
consisting, for example, of sugar or sugar alcohols and a mixture of ethanol, water,  
15 glycerol, propylene glycol and polyethylene glycol. If desired, such liquid  
preparations may contain coloring agents, flavoring agents, preservatives,  
saccharine and carboxymethyl cellulose or other thickening agents. Liquid  
preparations may also be prepared in the form of a dry powder to be reconstituted  
with a suitable solvent prior to use.

20 Solutions for parenteral administration may be prepared as a solution of a  
formulation of the invention in a pharmaceutically acceptable solvent. These  
solutions may also contain stabilizing ingredients, preservatives and/or buffering  
ingredients. Solutions for parenteral administration may also be prepared as a dry  
25 preparation to be reconstituted with a suitable solvent before use.

The total amount of active ingredient suitably lies in the range of from about 0.1 %  
(w/w) to about 95 % (w/w) of the formulation, suitably from 0.5 % to 50 % (w/w) and  
preferably from 1 % to 25 % (w/w).

30 The pharmaceutical formulations may contain between about 0.1 mg and about 1000  
mg of active ingredient, preferably between 1 mg and 100 mg of active ingredient.

The dose of the active ingredient to be administered will depend on the relevant indication, the age, weight and sex of the patient and may be determined by a physician. The dosage will suitably be in the range of from about 0.01 mg/kg to about 5 20 mg/kg, preferably between 0.1 mg/kg and 10 mg/kg.

The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, the route of administration, the age, weight and sex of the patient and may be determined by a 10 physician. In general, dosages, and especially oral and parenteral dosages, will be in the range of from about 0.1 to about 100 mg per day of active ingredient, preferably between 1 and 50 mg per day of active ingredient.

The following Example is intended to illustrate, but in no way limit the scope of the 15 invention.

#### EXAMPLE

A large-scale clinical trial was designed to examine the effect of the ACE inhibitor ramipril versus placebo in reducing cardiovascular events.

20 The study was conducted in 267 centres in 19 countries over a six year period and included 9,541 participants who are at high risk for cardiovascular events due to a history of previous ischaemic heart disease, stroke, peripheral arterial disease or individuals with diabetes.

25 The systolic blood pressure at inclusion of the patients was on average 138 mm Hg and thus the patients were normotensive at study start. After one month of therapy with either ramipril or placebo, the systolic blood pressure had decreased by 5.48 mm Hg and 1.59 mm Hg, respectively.

30 The primary endpoint of the study was myocardial infarction (MI), stroke and cardiovascular (CV) death (mortality).

The study was stopped early because of a very clear reduction in the combined endpoint of cardiovascular deaths, heart attacks and strokes in patients taking ramipril. In addition to the above benefits, there was also a reduction of between a 5 fourth and a fifth in the need for revascularisation procedures (such as coronary artery bypass graft surgery, balloon angioplasty, etc.) and diabetic complications.

There was a clear 32% reduction in the ramipril group in the number of patients who developed a stroke, and this is surprising since patients were normotensive when 10 recruited to the study.

The number of patients who developed CHF was significantly reduced by 21% in the ramipril group, which is unexpected since patients had no signs or symptoms of CHF at study start.

15 Equally surprising is the marked 36% reduction in the number of patients who developed diabetes in the ramipril group.

#### Abbreviations

20 ACE = angiotensin converting enzyme  
AT II = angiotensin II type 1 receptor  
CHF = congestive heart failure  
IDMM = insulin-dependent, diabetes mellitus  
JNC = Joint National Committee  
25 MI = myocardial infarction  
NIDDM = non-insulin-dependent diabetes mellitus  
WHO = World Health Organization

## CLAIMS

1. The use of an inhibitor of the renin-angiotensin system (RAS) or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the prevention of stroke.
2. The use of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the prevention of stroke in patients exhibiting normal or low blood pressure.
3. The use of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the prevention of diabetes.
4. The use of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the prevention of development of congestive heart failure (CHF) in patients with no preexisting CHF.
5. The use according to any previous claim, wherein the inhibitor of the RAS is an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II type 1 receptor (AT II) antagonist or a pharmaceutically acceptable derivative of any of these.
6. The use according to claim 5, wherein the ACE inhibitor or a pharmaceutically acceptable derivative thereof is selected from the group consisting of alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril,

quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat.

5

7. The use according to claim 6, wherein the ACE inhibitor is selected from the group consisting of ramipril, ramiprilat, lisinopril, enalapril and enalaprilat.
8. The use according to claim 5, wherein the AT II antagonist or a pharmaceutically acceptable derivative thereof is selected from the group consisting of candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan.
9. The use according to claim 8, wherein the AT II antagonist or a pharmaceutically acceptable derivative thereof is selected from the group consisting of candesartan and candesartan cilexetil.
10. A method of prevention of stroke, comprising administering a therapeutically effective amount of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof, to a patient in need of such prevention.
11. The method of prevention of stroke in patients exhibiting normal or low blood pressure, comprising administering a therapeutically effective amount of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof, to a patient in need of such prevention.
12. The method of prevention of diabetes, comprising administering a therapeutically effective amount of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof, to a patient in need of such prevention.
13. The method of prevention of development of CHF in patients with no preexisting CHF, comprising administering a therapeutically effective amount of an inhibitor of

30

the RAS or a pharmaceutically acceptable derivative thereof, to a patient in need of such prevention.

14. The method of prevention according to any one of claims 10 to 13, wherein the  
5 inhibitor of the RAS is an ACE inhibitor or an AT II antagonist or a pharmaceutically acceptable derivative of any of these.

15. The method of prevention according to claim 14, wherein the ACE inhibitor or a pharmaceutically acceptable derivative thereof is selected from the group consisting  
10 of alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril,  
20 temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat.

16. The method of prevention according to claim 15, wherein the ACE inhibitor is selected from the group consisting of ramipril, ramiprilat, lisinopril, enalapril and  
25 enalaprilat.

17. The method of prevention according to claim 14, wherein the AT II antagonist or a pharmaceutically acceptable derivative thereof is selected from the group consisting of candesartan, candesartan cilexetil, losartan, valsartan, irbesartan,  
30 tasosartan, telmisartan and eprosartan.

18. The method of prevention according to claim 17, wherein the AT II antagonist or a pharmaceutically acceptable derivative thereof is selected from the group consisting of candesartan and candesartan cilexetil.

5     19. A pharmaceutical formulation for use in the prevention of stroke, diabetes and/or CHF, comprising a therapeutically effective amount of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof.

10    20. The pharmaceutical formulation according to claim 19, wherein the inhibitor of the RAS is an ACE inhibitor or an AT II antagonist or a pharmaceutically acceptable derivative of any of these.

15    21. The pharmaceutical formulation according to claim 20, wherein the ACE inhibitor is selected from the group consisting of ramipril, ramiprilat, lisinopril, enalapril and enalaprilat.

20    22. The pharmaceutical formulation according to claim 20, wherein the AT II antagonist or a pharmaceutically acceptable derivative thereof is selected from the group consisting of candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan.

25    23. The pharmaceutical formulation according to any one of claims 19 to 22, in admixture with a pharmaceutically acceptable adjuvant, diluent and/or carrier.

30    24. The pharmaceutical formulation according to any one of claims 19 to 23, in unit dosage form.

      25. The use of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof, in the prevention of stroke, diabetes and/or CHF, by administering the inhibitor of the RAS or the pharmaceutically acceptable derivative thereof, to a patient in need of such prevention.

26. The use according to claim 25, wherein the inhibitor of the RAS is an ACE inhibitor or an AT II antagonist or a pharmaceutically acceptable derivative of any of these.

5    27. The use according to claim 26, wherein the ACE inhibitor is selected from the group consisting of ramipril, ramiprilat, lisinopril, enalapril and enalaprilat.

28. The use according to claim 26, wherein the AT II antagonist or a pharmaceutically acceptable derivative thereof is selected from the group consisting  
10    of candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan.



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**WO 01/15673 A3**

(54) Title: PHARMACEUTICAL FORMULATIONS AND USE THEREOF IN THE PREVENTION OF STROKE, DIABETES  
AND/OR CONGESTIVE HEART FAILURE

(57) Abstract: The present invention relates to use of an inhibitor of the renin-angiotensin system (RAS) or a pharmaceutically acceptable derivative thereof, particularly ramipril or ramiprilat, in the manufacture of a medicament for the prevention of stroke, diabetes and/or congestive heart failure (CHF). The present invention further relates to a method of prevention and/or treatment of stroke, diabetes and/or CHF, comprising administering a therapeutically effective amount of an inhibitor of the RAS or a pharmaceutically acceptable derivative thereof, particularly ramipril or ramiprilat, to a patient in need of such prevention and/or treatment.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/08341

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 A61K38/55 A61K31/00 A61K31/401 A61K31/4184 A61P9/04  
A61P9/10 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE, SCISEARCH

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 99 20260 A (MARTIN JOHN FRANCIS ;ERUSALIMSKY JORGE DANIEL (GB); EUROGENE LIMIT) 29 April 1999 (1999-04-29) abstract</p> <p>page 3, line 29 -page 4, line 5 page 6, line 27 - line 31 page 7, line 19 - line 21 page 8, line 1 - line 9 page 8, line 27 -page 9, line 19 page 10, line 4 - line 14 page 11, line 7 - line 11 page 12, line 5 -page 13, line 7 claims 1,2,15-22</p> <p>---</p> <p style="text-align: center;">-/-</p>	1,2, 5-11, 14-28

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
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- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

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# INTERNATIONAL SEARCH REPORT

Inte	rnational Application No
	PCT/EP 00/08341

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EP 0 474 438 A (SQUIBB &amp; SONS INC) 11 March 1992 (1992-03-11)</p> <p>abstract page 2, line 1 - line 31 page 2, line 46 - line 52 examples claims 1,11 ----</p>	1,2,5,6, 10,11, 14,15, 19,20, 23-26
X	<p>DATABASE WPI Week 199944 Derwent Publications Ltd., London, GB; AN 1999-520858 XP002166044 MASUDA YOSHINOBU, HONDA YAYOI, MINATO HISAO: "Inhibitor of cerebral vasospasm" &amp; JP 11 222439 A (DAINIPPON PHARM CO LTD), 17 August 1999 (1999-08-17) abstract ----</p>	1,5,6, 10,14, 15,19, 20,23-26
X	<p>WO 97 27745 A (TECHNOLOGY LICENSING CO L L C ;HAMMESFAHR WILLIAM M (US)) 7 August 1997 (1997-08-07)</p> <p>page 3, paragraph 1 - paragraph 3 page 4, paragraphs 1,3 page 5, paragraph 3 - paragraph 5 page 7, paragraph 3 -page 8, paragraph 1 page 1915, paragraph 2 page 1919, paragraph 4 claims 1,2,9,11 ----</p>	1,5-7, 10, 14-16, 20,21, 23-27
X	<p>OGIKU N ET AL: "Prophylactic effect of imidapril on stroke in stroke-prone spontaneously hypertensive rats." STROKE, (1993 FEB) 24 (2) 245-52., XP000997781 abstract page 245, column 1, paragraph 3 page 245, column 2, paragraph 4 -page 246, column 1, paragraph 1 figure 1 page 249, column 1, paragraph 3 -column 2, paragraph 1 page 251, column 1, paragraph 3 ----</p>	1,5-7, 10, 14-16, 19-21, 23-27
		-/--

**INTERNATIONAL SEARCH REPORT**

Inte onal Application No

PCT/EP 00/08341

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>STIER C T JR ET AL: "ENALAPRIL PREVENTS STROKE AND KIDNEY DYSFUNCTION IN SALT-LOADED STROKE-PRONE SPONTANEOUSLY HYPERTENSIVE RATS", HYPERTENSION (DALLAS), vol. 13, no. 2, 1989, pages 115-121, XP000997775 ISSN: 0194-911X abstract page 115, column 2, paragraph 3 -page 116, column 1, paragraph 1 figure 1 page 118, column 2, paragraph 1 page 120, column 2, paragraph 2</p>	1,5-7, 10, 14-16, 19-21, 23-27
X	<p>ROBERT MKW LEE, HONG WANG, JOHN S SMEDA: "Effects of perindopril on hypertension and stroke prevention in experimental animals", CAN. J. CARDIOL., vol. 10, no. Suppl D, November 1994 (1994-11), pages 33D-36D, XP000998206 abstract page 34D, column 1, paragraph 2 - paragraph 3 page 34D, column 2, paragraph 2 -column 3, paragraph 1 page 35D, column 2, paragraph 2 - paragraph 3 page 36D, column 3, paragraph 2</p>	1,5,6, 10,14, 15,19, 20,23-26
X	<p>J.E.F. REYNOLDS: "Martindale The Extra Pharmacopoeia", 1996, ROYAL PHARMACEUTICAL SOCIETY, LONDON XP002166043 page 863, column 2 -page 864, column 2 page 899, column 3 -page 900, column 1 page 940, column 3 -page 941, column 1</p>	19-21, 23,24
X	<p>EBERHARDT ROBERT T ET AL: "Angiotensin II receptor blockade: An innovative approach to cardiovascular pharmacotherapy.", JOURNAL OF CLINICAL PHARMACOLOGY, vol. 33, no. 11, 1993, pages 1023-1038, XP001019614 ISSN: 0091-2700 abstract page 1031, column 1, paragraph 4 -column 2, paragraph 2 page 1032, column 2, paragraph 2 -page 1033, column 1, paragraph 3</p>	1,3-5,8, 10, 12-14, 17,19, 20, 22-26,28
		-/-

# INTERNATIONAL SEARCH REPORT

Inte	rnational Application No
PCT/EP 00/08341	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>STIER CHARLES T JR ET AL: "Stroke prevention by losartan in stroke-prone spontaneously hypertensive rats." JOURNAL OF HYPERTENSION, vol. 11, no. SUPPL. 3, 1993, pages S37-S42, XP001019687</p> <p>Meeting on Losartan: An Orally Active Angiotensin II Antagonist; St. Paul de Vence, France; June 26-27, 1992</p> <p>ISSN: 0263-6352</p> <p>abstract</p> <p>page 537, column 1, paragraph 2</p> <p>page 538, column 1, paragraph 2 -</p> <p>paragraph 4</p> <p>page 540, column 1, paragraph 2 -page 541, column 1, paragraph 1</p> <p>---</p>	1,5-8, 10, 14-17, 19-28
X	<p>EP 0 331 014 A (THERA GES FUER PATENTE)</p> <p>6 September 1989 (1989-09-06)</p> <p>the whole document</p> <p>---</p>	3,5-7, 12, 14-16, 19-21, 23-27
X	<p>EP 0 426 066 A (SQUIBB &amp; SONS INC)</p> <p>8 May 1991 (1991-05-08)</p> <p>abstract</p> <p>page 2, line 1 -page 3, line 34</p> <p>examples</p> <p>claims</p> <p>---</p>	3,5-7, 12, 14-16, 19-21, 23-27
X	<p>US 5 190 970 A (PAN HENRY Y ET AL)</p> <p>2 March 1993 (1993-03-02)</p> <p>abstract</p> <p>column 1, line 10 - line 17</p> <p>column 4, line 26 - line 39</p> <p>column 9, line 63 -column 11, line 24</p> <p>examples</p> <p>claims</p> <p>---</p>	3,5-7, 12, 14-16, 19-21, 23-27
X	<p>DE 43 08 504 A (KNOLL AG)</p> <p>22 September 1994 (1994-09-22)</p> <p>the whole document</p> <p>----</p> <p>-/-</p>	3,5,6, 12,14, 15,19, 20,23-26

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/08341

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 266 583 A (OHTAWA MASAKATSU) 30 November 1993 (1993-11-30)  abstract column 1, line 34 - line 55 column 3, line 20 - line 36 column 3, line 56 -column 4, line 20 column 4, line 67 -column 5, line 7 examples ---	3-5, 8, 12-14, 17, 19, 20, 22-26, 28
X	US 5 308 846 A (ALLEN ERIC E ET AL) 3 May 1994 (1994-05-03)  abstract column 1, line 11 - line 44 column 18, line 14 - line 19 column 20, line 2 - line 59 example 7 claim 6 ---	3-5, 12-14, 19, 20, 23-26
X	BLUMENTHAL MEL: "Treatment of congestive heart failure: Experience with fosinopril." AMERICAN JOURNAL OF HYPERTENSION, vol. 10, no. 10 PART 2, 1997, pages 289S-298S, XP001019673 ISSN: 0895-7061 abstract page 290S, column 2, paragraph 2 page 297S, column 1, paragraph 3 ---	4-7, 13-16, 19-21, 23-27
X	EP 0 795 327 A (PFIZER) 17 September 1997 (1997-09-17)  abstract page 2, line 5 - line 14 page 4, line 19 - line 42 page 7, line 57 -page 8, line 20 claims 8, 9, 11 ---	4-7, 13-16, 19-21, 23-27
X	EP 0 241 201 A (MERCK & CO INC) 14 October 1987 (1987-10-14)  the whole document ---	4-7, 13-16, 19-27
		-/-

**INTERNATIONAL SEARCH REPORT**

Inte onal Application No

PCT/EP 00/08341

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 96 24373 A (SEARLE &amp; CO ;PEREZ ALFONSO T (US); MACLAUGHLAN TODD E (US)) 15 August 1996 (1996-08-15)</p> <p>abstract page 1, line 6 - line 17 page 7, line 4 - line 25 page 9, line 27 -page 11, line 5 page 31, line 11 - line 25 examples claims 1,4,5,9,11,17,18,26,28,29</p>	4-7, 13-16, 19-21, 23-27
X	<p>WO 93 20839 A (BRIGHAM &amp; WOMENS HOSPITAL) 28 October 1993 (1993-10-28)</p> <p>abstract page 5, paragraph 1 page 6, paragraph 8 -page 8, paragraph 1 page 9, paragraph 3 page 11, paragraph 1 - paragraph 2 page 12, paragraph 3 -page 13, paragraph 1 page 14, paragraph 3 -page 15, paragraph 1 page 27, paragraph 2 -page 28, paragraph 3 page 34, paragraph 1 claims 2,4-6,18,19,25</p>	4-6,8, 13-15, 17,19, 20, 22-26,28
X	<p>GB 2 308 064 A (MERCK &amp; CO INC) 18 June 1997 (1997-06-18)</p> <p>abstract page 1, line 26 - line 31 page 6, line 1 - line 28 page 38, line 16 -page 39, line 26 claims 6,7,9</p>	4-9, 13-28
X	<p>WO 97 49392 A (MERCK &amp; CO INC ;SWEET CHARLES S (US); CHEN TZYY SHOW H (US); GROSS) 31 December 1997 (1997-12-31)</p> <p>abstract page 3, line 10 -page 4, line 18 page 6, line 19 - line 22 page 8, line 1 - line 5 page 15, line 11 - line 17 claims 1-11,21</p>	4-8, 13-17, 19-28
X	<p>EP 0 540 209 A (UPJOHN CO) 5 May 1993 (1993-05-05)</p> <p>abstract page 2, line 1 - line 23 page 5, line 41 - line 46 page 8, line 56 -page 9, line 3 page 45, line 41 -page 46, line 2 claims 8-12</p>	4,5,13, 14,19, 20,23-26

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/08341

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 747 050 A (SQUIBB BRISTOL MYERS CO) 11 December 1996 (1996-12-11)  abstract page 2, line 1 - line 30 page 6, line 31 - line 37 claim 1 ----	4,5,8, 13,14, 17,19, 20, 22-26,28
X	US 5 506 361 A (KOH KEIKO ET AL) 9 April 1996 (1996-04-09)  abstract column 1, line 14 - line 20 column 2, line 41 - line 50 column 3, line 6 - line 57 column 13, line 62 -column 15, line 27 ----	4,5,13, 14,19, 20,23-26
X	NAKAMURA FUMIAKI ET AL: "Chronic administration of angiotensin II receptor antagonist, TCV-116, in cardiomyopathic hamsters." AMERICAN JOURNAL OF PHYSIOLOGY, vol. 267, no. 6 PART 2, 1994, pages H2297-H2304, XP001019610 ISSN: 0002-9513 abstract page H2297, column 1, paragraph 1 -column 2, paragraph 1 page H2299, column 2, paragraph 2 -page H2300, column 2, paragraph 1 page H2301, column 1, paragraph 1 page H2303, column 1, paragraph 2 ----	4,5,13, 14,19, 20,23-26
X	K. PARFITT: "Martindale - The complete drug reference - Thirty-second Edition" 1999 , PHARMACEUTICAL PRESS , LONDON UK XP002176301 page 836, column 1 page 865, column 3 page 891, column 3 -page 892, column 1 page 899, column 1 page 951, column 3 page 960, column 2 -column 3 ---- -/-	19,20, 22-24

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/08341

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 98 30216 A (BEERE POLLY A ;CHANG PAUL I (US); MERCK &amp; CO INC (US); PITT BERTRA) 16 July 1998 (1998-07-16)</p> <p>abstract  page 1, line 6 - line 10  page 3, line 34 -page 4, line 11  page 5, line 14 - line 34  page 21, line 26 -page 22, line 8  page 33, line 1 - line 27  page 44, line 6 - line 27  page 65, line 1 - line 19  claims 1-3,11,12,16-18,23,24,29,30</p> <p>---</p>	4,5,8,9, 13,14, 17-20, 22-26,28
P,X	<p>DE 199 13 528 A (SANOL ARZNEI SCHWARZ GMBH) 29 June 2000 (2000-06-29)</p> <p>abstract  column 1, line 1 - line 67  column 2, line 37 - line 42  example 1  column 3, line 58 - line 61  column 4, line 2 - line 5  claim 1</p> <p>---</p>	1,5,6, 10,14, 15,19, 20,23-26
P,X	<p>WO 99 44590 A (KAMEI SHIGERU ;SAIKAWA AKIRA (JP); IGARI YASUTAKA (JP); INADA YOSH) 10 September 1999 (1999-09-10)</p> <p>abstract  page 1, line 6 - line 9  page 2, line 35 -page 3, line 5  page 5, line 20 - line 32  page 33, line 4 - line 11  page 44, line 23 - line 30  claims 1,21,24</p> <p>---</p>	3,5,12, 14,19, 20,23-26
P,X	<p>WO 00 02543 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); GASPARO MARC DE (C) 20 January 2000 (2000-01-20)</p> <p>abstract  page 1, paragraph 1 - paragraph 2  page 4, paragraph 1  page 7, paragraph 3 -page 9, paragraph 3  page 10, paragraph 3  claims 1,4,5,9</p> <p>---</p> <p>-/-</p>	1,3-5, 8-10, 12-14, 17-20, 22-26,28

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/08341

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	<p>WO 00 71751 A (MYRIAD GENETICS INC) 30 November 2000 (2000-11-30)</p> <p>abstract page 5, line 5 - line 22 page 25, line 31 -page 26, line 19 claims 8-13</p> <p>-----</p>	<p>3,5,8, 12,14, 17,19, 20, 22-26,28</p>
E	<p>WO 01 15674 A (AVENTIS PHARMA GMBH) 8 March 2001 (2001-03-08)</p> <p>page 1, line 6 - line 15 page 3, line 6 - line 29 page 4, line 11 -page 5, line 10 page 6, line 1 -page 8, line 21 claims 1,5,7-11,16,20-26</p> <p>-----</p>	<p>1,3-10, 12-28</p>

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 00/08341

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  

Although claims 10-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  

see FURTHER INFORMATION sheet PCT/ISA/210
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-5, 10-14, 19, 20, 23-26 relate to a compound which actually is not well-defined. The use of the definitions "an inhibitor of the renin-angiotensin system or a pharmaceutically acceptable derivative thereof", "an angiotensin converting enzyme inhibitor or a pharmaceutically acceptable derivative thereof" and "an angiotensin II type 1 receptor (AT II) antagonist or a pharmaceutically acceptable derivative of any of these" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible. Moreover, present claims 6 and 15 relate to a very large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the ACE-inhibitors particularly preferred, as disclosed in claims 7, 16, 21 and 27 and in the example p. 10, namely ramipril, ramiprilat, lisinopril, enalapril and enalaprilat, and to the AT II antagonists mentioned in claims 8, 9, 17, 18, 22, 28.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1, 2, 5-7, 10, 11, 14-16, 19-21, 23-27 (partially)

Use of an angiotensin converting enzyme (ACE) inhibitor or a derivative thereof for the prevention of stroke.

2. Claims: 1, 2, 5, 8-11, 14, 17-20, 22-26, 28 (partially)

Use of an angiotensin II type 1 receptor (AT II) antagonist or a derivative thereof for the prevention of stroke.

3. Claims: 3, 5-7, 12, 14-16, 19-21, 23-27 (partially)

Use of an angiotensin converting enzyme (ACE) inhibitor or a derivative thereof for the prevention of diabetes.

4. Claims: 3, 5, 8, 9, 12, 14, 17-20, 22-26, 28 (partially)

Use of an angiotensin II type 1 receptor (AT II) antagonist or a derivative thereof for the prevention of diabetes.

5. Claims: 4-7, 13-16, 19-21, 23-27 (partially)

Use of an angiotensin converting enzyme (ACE) inhibitor or a derivative thereof for the prevention of the development of congestive heart failure.

6. Claims: 4, 5, 8, 9, 13, 14, 17-20, 22-26, 28 (partially)

Use of an angiotensin II type 1 receptor (AT II) antagonist or a derivative thereof for the prevention of the development of congestive heart failure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

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Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9920260	A	29-04-1999		AU 9453398 A CN 1279606 T EP 1023067 A NO 20001979 A PL 340838 A US 6107420 A	10-05-1999 10-01-2001 02-08-2000 13-06-2000 26-02-2001 22-08-2000
EP 0474438	A	11-03-1992		AU 8342591 A CA 2048699 A HU 59315 A IE 912821 A JP 4279524 A ZA 9107023 A	12-03-1992 05-03-1992 28-05-1992 11-03-1992 05-10-1992 27-05-1992
JP 11222439	A	17-08-1999		NONE	
WO 9727745	A	07-08-1997		AU 2252297 A	22-08-1997
EP 0331014	A	06-09-1989		AU 3091889 A DK 99989 A JP 1261334 A	07-09-1989 03-09-1989 18-10-1989
EP 0426066	A	08-05-1991		CA 2026686 A JP 3153633 A	01-05-1991 01-07-1991
US 5190970	A	02-03-1993		US 5130333 A	14-07-1992
DE 4308504	A	22-09-1994		AU 6376694 A WO 9421285 A	11-10-1994 29-09-1994
US 5266583	A	30-11-1993		GB 2270074 A	02-03-1994
US 5308846	A	03-05-1994		US 5202322 A US 5256667 A CA 2079079 A EP 0534706 A JP 6073024 A	13-04-1993 26-10-1993 26-03-1993 31-03-1993 15-03-1994
EP 0795327	A	17-09-1997		AU 713842 B AU 1630797 A CA 2199888 A HU 9700588 A JP 2918512 B JP 10007566 A US 5948799 A ZA 9702228 A	09-12-1999 18-09-1997 15-09-1997 28-05-1999 12-07-1999 13-01-1998 07-09-1999 14-09-1998
EP 0241201	A	14-10-1987		AU 7110387 A CA 1288351 A DK 174087 A JP 62242626 A	08-10-1987 03-09-1991 08-10-1987 23-10-1987
WO 9624373	A	15-08-1996		AU 5354196 A BR 9604882 A CA 2212713 A EP 0808172 A JP 11507012 T	27-08-1996 19-05-1998 15-08-1996 26-11-1997 22-06-1999

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/08341

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9320839	A	28-10-1993	US	5977160 A	02-11-1999
			US	5972990 A	26-10-1999
			AU	4281093 A	18-11-1993
			CA	2117782 A	28-10-1993
			EP	0641218 A	08-03-1995
			JP	7505884 T	29-06-1995
			US	5952305 A	14-09-1999
GB 2308064	A	18-06-1997	NONE		
WO 9749392	A	31-12-1997	AU	724576 B	28-09-2000
			AU	3571097 A	14-01-1998
			CA	2257946 A	31-12-1997
			EP	0910375 A	28-04-1999
			JP	2000513356 T	10-10-2000
			US	6087386 A	11-07-2000
EP 0540209	A	05-05-1993	JP	6107661 A	19-04-1994
			AT	140458 T	15-08-1996
			AU	661346 B	20-07-1995
			AU	2759292 A	21-05-1993
			CA	2118802 A	29-04-1993
			DE	69212331 D	22-08-1996
			DE	69212331 T	09-01-1997
			DK	609289 T	25-11-1996
			EP	0609289 A	10-08-1994
			ES	2091489 T	01-11-1996
			GR	3021143 T	31-12-1996
			JP	7500336 T	12-01-1995
			MX	9206157 A	31-05-1994
			WO	9308193 A	29-04-1993
			US	5442062 A	15-08-1995
EP 0747050	A	11-12-1996	AU	702651 B	25-02-1999
			AU	5476396 A	19-12-1996
			CA	2177772 A	08-12-1996
			CN	1144656 A	12-03-1997
			CZ	9601634 A	11-12-1996
			HU	9601564 A	28-09-1998
			JP	3162626 B	08-05-2001
			JP	8333253 A	17-12-1996
			NO	962387 A	09-12-1996
			NO	20004743 A	09-12-1996
			NZ	286612 A	25-03-1998
			NZ	329547 A	26-06-1998
			PL	314670 A	09-12-1996
			SG	49956 A	15-06-1998
			US	5994348 A	30-11-1999
US 5506361	A	09-04-1996	AU	650342 B	16-06-1994
			AU	1784892 A	21-12-1992
			CA	2106968 A	09-11-1992
			EP	0586466 A	16-03-1994
			JP	5112533 A	07-05-1993
			JP	6507620 T	01-09-1994
			MX	9202132 A	01-04-1993
			WO	9219211 A	12-11-1992

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No

PCT/EP 00/08341

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9830216	A 16-07-1998	AU 729881	B	15-02-2001
		AU 6021898	A	03-08-1998
		CN 1249682	T	05-04-2000
		EE 9900278	A	15-02-2000
		EP 0966282	A	29-12-1999
		HU 0000108	A	28-04-2001
		JP 2000508347	T	04-07-2000
		NO 993399	A	09-09-1999
		SK 92899	A	14-08-2000
		US 6201002	B	13-03-2001
		ZA 9800163	A	10-07-1998
DE 19913528	A 29-06-2000	NONE		
WO 9944590	A 10-09-1999	AU 2745199	A	20-09-1999
		BR 9908474	A	05-12-2000
		CN 1291888	T	18-04-2001
		EP 1058541	A	13-12-2000
		JP 11315034	A	16-11-1999
		LV 12585	A	20-12-2000
		LV 12585	B	20-03-2001
		NO 20004350	A	03-10-2000
WO 0002543	A 20-01-2000	AU 5034999	A	01-02-2000
		BR 9912021	A	03-04-2001
		EP 1096932	A	09-05-2001
		NO 20010113	A	09-03-2001
WO 0071751	A 30-11-2000	AU 5016200	A	12-12-2000
WO 0115674	A 08-03-2001	AU 7649100	A	26-03-2001